UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR#: 0050172

MEMORANDUM

DATE: March 19, 2002

SUBJECT: ***ENFROST* (Urea, End-Use Formulation):** Toxicology Chapter of the Tolerance Reassessment Eligibility Decision (TRED) for the Active Ingredient Pesticide, Urea.

EPA ID NO.:	PC Code: 085702	PRAT Case Number: 819300
	DP Barcode: D274740	Reregistration Case Number: 4096
	Submission Number: S596788	CAS Registry Number: 57-13-6

FROM: Michelle M. Centra, Pharmacologist
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THRU: Catherine Eiden, Branch Senior Scientist
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TO: Joseph Nevola, Chemical Review Manager
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and

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The Health Effects Division (HED) has conducted a reassessment of the available toxicity data for the frost protectant pesticide, urea. Since the Agency established a permanent exemption from the requirement of a tolerance for residues of urea in or on various agricultural commodities (effective August 23, 1995) prior to passage of the Food Quality Protection Act

(FQPA, 1996), a revised hazard characterization, including special sensitivity to infants and children is required.

This memorandum contains the toxicology chapter for urea tolerance reassessment eligibility decision (TRED) document. An electronic copy of this document is available and stored under the following Toxicology Record (TXR) Number: 0050172.

The following supporting documents used to generate the TRED toxicology chapter for urea are also included as attachments:

Health Effects Division Documents

1. Review of Six Acute Toxicity Studies and Two Literature Reviews on Urea. Review PP# 8F3662 (Memorandum: S. Stolzenberg, June 30, 1989).
2. Petition for use of Urea on crops as a frost protection agent. Request to waive certain toxicity data requirements. PP# 8F3662. (Memorandum: D. Ritter, February 24, 1989).
3. Urea (Enfrost); Reclassification of Six Acute Toxicity Studies from Supplementary to Guideline (Memorandum: R. Landolt, June 17, 1991).
4. Data waiver request for urea as an active ingredient for use as a frost protectant (Memorandum: J. Stewart, April 17, 2001).
5. *ENFROST* (Urea, End-Use Formulation): Re-evaluation of mammalian acute toxicity studies (OPPTS Test Guidelines 870.1100, 870.1200, 870.1300, 870.2400, 870.2500, and 870.2600) submitted by Unocal Corporation in Support of Registration. PC Code: 085702. DP Barcode: D277687. Submission Number: S596788. (Memorandum: M. Centra, March 10, 2002).

Additional Supporting Documents

6. Food and Drug Administration, Department of Health and Human Services, code of federal regulations (Parts 170 to 199, Revised as of April 1, 2001). 21 CFR Part 184.1923; Urea, page 549.
7. U.S. Environmental Protection Agency/Office of Pesticide Programs and Toxic Substances, Pesticide Fact Sheet (August 23, 1995).
8. Environmental Protection Agency, Federal Register Vol. 60, No. 163, Rules and Regulations. 40 CFR Part 180; Urea: Exemption From the Requirement of a Tolerance [PP-8F3662/R1176; FRL-4178-2] RIN 2070-AB78 (August 23, 1995).

cc (with attachments): M. Centra (HED/RRB III), C. Eiden (HED/RRB III), R. Daiss (HED/RRB IV), J. Nevola (SRRD/SRB), R. McNally (SRRD/SRB).

UREA

PC Code: 085702

Toxicology Disciplinary Chapter for the Tolerance Reassessment Document
TXR#: 0050172

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Prepared by: Michelle M. Centra, Pharmacologist
Date completed: October 2, 2001

INTRODUCTION

The active ingredient, urea, has GRAS (Generally Recognized as Safe) status as a direct food additive under Title 21 Code of Federal Regulations (CFR) 184.1923. The FDA affirmation of urea as safe was made by the Select Committee on GRAS Substances [a group of qualified scientists chosen by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB)] in accordance with FDA guidelines. In the opinion of the members of this Committee " no evidence in the available information on urea demonstrates, or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future".

Urea is also exempt from the requirement of a tolerance under 40 CFR 180.1001(c) as an inert ingredient and sometimes as an active ingredient in formulations applied to growing crops or crops after harvest based upon the following considerations: (1) the amount of urea used as an active ingredient is similar to that permitted for the inert ingredient use (2) urea is a normal body constituent and is constantly being produced during amino acid and protein metabolism (3) urea is a naturally occurring crop/plant constituent that is found in commonly consumed foods (4) several grams of urea per kilogram body weight can be ingested by nonruminants, including man, without untoward effects (5) most of the nitrogen consumed in food is excreted in the form of urea. A 70 kg individual consuming a normal diet will excrete an average of 25 g urea daily (6) therapeutically, in humans, urea has been used as an osmotic diuretic to reduce blood pressure, intraoccular pressure and intracranial pressure, as a dermatologic agent to debride necrotic and infected tissues, as a topical anesthetic for the mouth and throat, in the treatment of sickle-cell anemia, and in neurosurgical procedures with few adverse effects and (7) urea has FDA-affirmed Generally Recognized as Safe (GRAS) status.

In 1995, the EPA granted a permanent exemption from the requirement of a tolerance for residues of the frost protectant urea in or on various raw agricultural commodities. Since this decision was made prior to the passage of the Food Quality Protection Act (FQPA, 1996), a revised hazard characterization that includes special sensitivity to infants and children is required for the urea Tolerance Reassessment Eligibility Decision (TRED) document.

HED's Toxicology Science Advisory Council (TOX SAC) met on March 22, 2001 to consider a request to reaffirm the toxicology data waivers granted in 1989 for the use of urea as a frost protectant on food crops (Memoranda: Ritter to Wilson, dated 2/23/89 and Stolzenberg to Rossi, dated 6/13/89). The TOX SAC examined the 1978 Monograph on urea by the FDA Select Committee on GRAS Substances of the Life Sciences Research Office (LSRO), Federation American Society of Experimental Biology (FASEB), as well as, the HED One Liners, and the 21 CFR Citation 184.1923, which affirms urea as GRAS as a direct human food ingredient. It was noted that the FDA GRAS affirmation was without limitations other than the current good manufacturing practice. There are no prior sanctions for this chemical. Based on the information presented to the TOX SAC, the Council voted unanimously to reaffirm the toxicology data waivers, and to recommend that no further toxicity studies be required. The reaffirmed toxicology data waivers are listed in Table 1.

TABLE 1. HED REAFFIRMED TOXICOLOGY DATA WAIVERS	
Study Type	**Guideline Number**
90 Day Feeding Study in Rodents	870.3100
90 Day Feeding Study in Nonrodents	870.3150
21 Day Dermal Toxicity Study	870.3200
90 Day Dermal Toxicity Study	870.3250
90 Day Inhalation Toxicity Study	870.3465
Chronic Feeding Studies in Rodents and Nonrodents	870.4100
Carcinogenicity Studies in Two Mammalian Species	870.4200
Developmental Toxicity Studies in Rodents and Nonrodents	870.3700
Multigeneration Reproduction Study in Rodents	870.3800
Battery of Mutagenicity Studies	870.5100; 870.5300; 870.5385; 870.5375 and 870.5395
General Metabolism Study	870.7485

From the available animal studies and human exposure, the EPA has concluded that toxicity from exposure to urea is low. This conclusion agrees with that advanced in 1978 by the Select Committee on GRAS substances of the Life Sciences Research Office. The following hazard characterization includes an extensive review of literature toxicology data in numerous species, including man, to support the view that urea is safe in reasonably anticipated patterns of usage.

HAZARD CHARACTERIZATION

With the exception of six acute toxicity studies submitted by the Registrant for the Enfrost formulation, the urea toxicology data base is primarily comprised of the available literature data. These data are considered complete to assess the potential hazard to humans, including special sensitivity of infants and children.

Acute Toxicity

Ruminants are much more sensitive to urea than are nonruminants. The sudden ingestion of 116 g (about 230 mg per kg) by cattle or 10 g (about 160 mg per kg) by sheep, undiluted by feed, has resulted in labored breathing, tetanic spasms and prostration within 30 minutes.

Among nonruminants, the acute toxicity of urea appears to be relatively low. The lethal dose (LD_{50}) for an oral exposure in rats was 14,500 mg/kg which would be equivalent to a two pound ingestion of urea by an average size adult human. The acute toxicity of urea has also been evaluated in rabbits, cattle, sheep, dogs, guinea pigs, frogs, pigeons and ponies by oral, subcutaneous and intravenous exposures. Urea was slightly toxic in these mortality studies. Acute toxicity data are shown in Table 2.

TABLE 2. ACUTE TOXICITY OF UREA

Animal	Route of Administration	Results
Rabbit	Oral	LD_{50} = 5000 mg/kg
	Gavage	LD_{50} = 5000
	Subcutaneous	LD_{50} = 3000-9000
	Intravenous	LD_{50} = 7320
	Intravenous	LD_{50} = 6310
Cattle	Oral	MLD_{50} = 510
	Oral	MLD_{50} = 600-1080
Pony	Gavage	LD_{50} = 3310-3610
Sheep	Oral	MLD_{50} = 510
Dog	Subcutaneous	LD_{50} = 3000-9000
	Intravenous	LD_{50} = 3000
	Intravenous	MLD_{50} > 10,000
Guinea pig	Intravenous	LD_{50} = 4800
Frog	Subcutaneous	LD_{50} = 600-1000
Pigeon	Subcutaneous	LD_{50} = 16,000

LD_{50} = a statistically derived expression of a single dose of material that can be expected to kill 50 percent of the animals.

MLD_{50} = the median single dose of a material that can be expected to kill 50 percent of the animals.

No serious reactions have been recorded in humans with proper parenteral urea therapy. In man, intravenous administration of 1 g per kg body weight urea to reduce intracranial pressure may cause headaches (similar to those following lumbar puncture), nausea, vomiting, mental confusion, hyperthermia, nervousness, tachycardia and occasionally, fainting. However, these adverse effects can be minimized by slow infusion. Urea is also used orally as a diuretic in daily doses of 40 to 100 g (0.7 to 1.6 g/kg). Two to 3 g/kg body weight have been given orally to normal volunteers with no reported untoward effects, except significant diuresis.

The therapeutic effectiveness of urea in sickle-cell anemia is still controversial, but its use provides additional data on its possible acute toxicity. Massive doses of urea have been injected intravenously into patients during sickling crisis. The total dose of urea varied from 2.6 g/kg body weight injected over a 10-hour period to a maximal dose of 6.0 g per kg administered within 12 to 24 hours. The injection fluid was 10 or 15 percent urea dissolved in 10 percent invert sugar solution. Adverse effects were not serious, consisting mainly of diuresis, headache and vein irritation. However, the diuresis was considerable. In one instance, the urinary output over an 18-hour period was more than 28 liters.

In man, urea may cause redness and irritation to the skin. Urea is considered a mild skin irritant when applied to human skin intermittently (22 mg urea) over a 3 day period. With parenteral therapy, urea is more irritating to skin than mannitol, another popular osmotic agent. Although chemical phlebitis and thrombosis near the injection/infusion site are rare, urea may cause pain and some tissue injury if excessive bleeding occurs.

Many commercially available moisturizers contain urea (10-15 %) as an active ingredient and it is believed to be of importance in the prophylaxis and treatment of dry skin disorders. No systemic side-effects have been noted with use of skin moisturizers. All reported adverse effects were classified non-serious; some topical preparations caused disagreeable sensations such as smarting, stinging and itching immediately after application, however, these preparations did not cause skin irritation in the ordinary sense and usually did not cause damage to the skin barrier. The active ingredient, urea, has been shown to produce burning reactions on lesional forearm skin at concentrations similar to those present in creams.

Prolonged eye contact with high concentrations of urea may cause irritation (redness) and damage. Exposure of rabbit eyes to a saturated urea solution resulted in loss of epithelium from the cornea after five minutes contact and produced a grayness of the corneal stroma. One hour exposure to a 40% urea solution in rabbit eyes resulted in similar corneal effects with recovery in several weeks. Injection of 0.2 ml of a 10 M urea solution (0.12 grams) into the vitreous humor of rabbits caused inflammation, chorioretinitis and retinal degeneration.

Toxicity studies conducted with the Enfrost formulation (urea, 43.5% a.i.) submitted by the registrant show low toxicity following acute exposure (Table 3). Enfrost has a low order of acute toxicity via oral, dermal and inhalation routes (Toxicity Category III or IV) and produces slight irritation to the eyes and skin (Toxicity Category IV). Enfrost is not a dermal sensitizer.

TABLE 3. ACUTE TOXICTY PROFILE FOR ENFROST (Urea, 43.5% a.i.)				
Guideline	**Study Type (Date)**	**MRID**	**Results**	**Tox. Cat.**
870.1100 (§81-1)	Acute Oral-Rat (5/11/88)	40733304	LD_{50} > 5000 mg/kg	IV
870.1200 (§81-2)	Acute Dermal-Rabbit (5/11/88)	40733305	LD_{50} > 2000 mg/kg	III
870.1300 (§81-3)	Acute Inhalation-Rat (5/11/88)	40733301	LC_{50} > 4.8 mg/L	III
870.2400 (§81-4)	Primary Eye Irritation-Rabbit (5/11/88)	40733302	Slight eye irritant	IV
870.2500 (§81-5)	Primary Dermal irritation-Rabbit (5/11/88)	40733306	Slight dermal irritant	IV
870.2600 (§81-6)	Dermal Sensitization-Guinea pig (5/11/88)	40733303	Non sensitizer	N/A

Subchronic Toxicity

Toxicity to urea is dependent on species, body size, nutritional status, rate of feeding and nature of the diet. Most of these studies have been conducted with ruminants. The American Feed Control Officials recommend that the amount of urea fed to cows not exceed 3 percent of the total grain ration, which represents about 0.45 g/kg/day. Various reports indicate that sheep can ingest 50 to 100 g (about 0.8 to 1.6 g/kg) urea daily with no harmful effects when properly mixed with feed.

In a subchronic toxicity study, urea produced no severe toxicity in dogs injected subcutaneously with 30-40 ml/kg/day of 10% urea solution for 45 days. With plasma levels ranging from 200-700 mg/100 ml (10-30 fold above normal), the only clinical symptoms observed were drowsiness and diuresis. Necropsy indicated no adverse organ pathology. Therefore, urea was not considered an important uremic toxin in dogs with normal renal function. However, studies of nephrectomized dogs in which urea levels of 540-1690 mg/100 ml of extracellular fluid were maintained for 10 days by means of intermittent peritoneal lavage, severe uremic signs, such as weakness and anorexia followed by retching, vomiting, diarrhea, reduced body temperature and culminating in deep torpor or coma were evident.

Rats fed rations containing 2 to 25 percent urea (2- 25 g/kg body weight daily) for periods up to 190 days showed systemic toxicities. Even at the lower levels of urea ingestion, weight loss and suppression of sexual function resulted. Rats receiving14 percent urea in their diet and deprived of water died within a few days. If water were allowed, animals survived for 20 to 76 days when fed the 20 percent urea supplement and 12 days when fed the 25 percent urea supplement. Anemia and renal hypertrophy were also observed in some these animals. However, it is difficult to interpret these findings because of the number of rats tested per treatment group was small (often 1 to 3) and no data were given on the actual food intake. The extreme weight loss observed in rats suggests that starvation was most likely the result of decreased palatability of the animal feed containing urea.

In contrast, severe forms of uremia are not manifested in dialysis patients with blood urea concentrations above 300 mg/100 ml. High blood concentrations of 181 to 600 mg urea/100 ml were maintained by intermittent dialysis in three patients suffering from advanced renal failure for periods of 7 to 90 days. When the urea concentration was kept below 300 mg per 100 ml, no untoward effects were noted although this level is about 10 times greater than normal. Concentrations above 300 mg per 100 ml were associated with malaise, vomiting, bleeding tendency and headache. However, the more severe gastrointestinal, cardiovascular, mental and neurologic changes of uremia were not observed.

In eight patients with sickle cell disease, 40 to120 g (0.6 to 2.0 g/kg) urea was administered orally in divided doses each day for periods of 3 weeks to 9 months. The blood urea concentrations of the patients approximately doubled during the test periods. While the patients were ingesting urea, there was a slight decrease in blood volume, probably resulting from the chronic osmotic diuresis induced by the urea. The most obvious effects of the urea intake were thirst and diuresis and two patients were unable to complete the study because of nausea and vomiting.

Chronic Toxicity and Carcinogenicity

No toxicities from urea have been reported in humans after chronic exposures. One year feeding studies in male and female C57B1/6 mice and Fisher 344 rats reported no evidence of treatment-related cancer at doses up to 4.5% of the diet. Slight increases in the incidence of lymphomas occurring in mid-dose female mice as well as interstitial cell adenomas of the testes occurring in high-dose male rats, were not considered biologically significant in this study.

Earlier studies also indicated no evidence of urea tumorigenicity. Doses of 10 to 50 mg urea (0.5 - 2.5 g/kg were injected subcutaneously in mice (Strain A) over a period of 11 months. No tumors were evident after 15 months. Weekly intraperitoneal injections of 400 mg/kg urea administered over a 13 week interval produced no lung adenomas in the sensitive mouse strain (Strain A).

Developmental and Reproductive Toxicity

In a developmental toxicity study, pregnant Wistar rats receiving a twice-daily dose of 25 g/kg urea by gastric intubation for 14 days produced healthy offspring with no reported evidence of teratogenic effects. Additionally, pregnant cows, which recovered from urea toxicity, exhibited no effects on reproductive performance nor were the calves affected. No effect on the number of calves born, birth weight, weaning weight of calves or rebreeding performance was observed in these animals when treated acutely with urea (0.44 g/kg) and kept under regular management for

12 months. However, immersion of frog eggs in 1.25% urea and injection of chick embryos with 50-900 mg urea have produced some evidence of neural, vascular or cardiac abnormalities.

Urea has been evaluated in monkeys and humans for its ability to induce abortion. In humans, intra-amniotic injection of 80 grams "Ureaphil"/210 ml in 5% dextrose was effective in inducing abortion at 14 weeks without adverse effects to the mother. The mode of action is similar to the hyperosmolar effect of large doses of hypertonic saline and dextrose where a highly localized hyperosmolar solute passes from the amniotic fluid into the fetus causing death. Such high intrauterine exposures would not occur from environmental exposure to urea. Urea is currently classified by FDA in category C for therapeutic use ("Safety for use during pregnancy has not been established").

Mutagenicity

Several *in vitro* studies have reported that urea is associated with chromosomal aberrations in human leukocytes, hamster fibroblasts and lung cells. All of these studies were conducted with urea concentrations ranging from 50 mM to 8 M. At physiological levels (1mM), urea causes no chromosome effects. However, at concentrations of urea greater than or equal to 50mM, the production of chromosome fragmentation is probably due to a non-specific, hyperosmolarity effect on cell division and not a direct effect of the urea molecule. Sodium phosphate, another normal body fluid constituent also produces chromosomal damage at 50 mM concentrations.

Absorption, Metabolism, and Excretion

Urea is extremely soluble in water and oral doses are rapidly absorbed and distributed through the most body tissues and fluids, in proportion to their water content. However, the penetration of urea into fatty tissue such as the brain is lower than for most other tissues. The colon has been reported to be relatively impermeable to urea. When urea solutions were introduced into the colon in men, urea concentration in the blood remained unchanged.

In pregnant rats injected subcutaneously with urea, it was found that not only had urea penetrated rapidly into maternal tissues and organs but that it also readily passed through the placenta. Within 30 minutes after injection, the urea content of maternal muscle and liver had increased approximately threefold over the control value, and the fetal concentration had doubled. Two hours after injection, the fetus and the maternal liver and muscle contained equal concentrations of urea. When sheep were fed 40 g of urea with 40 g of glucose, the urea content of portal blood doubled within 15 minutes.

In man, too, the absorption of urea is very rapid. Blood urea concentration was found to reach a peak, generally within 30 minutes after oral administration. Similar results were reported in human volunteers; serum urea levels doubled within 20 minutes after receiving 30 g of urea by mouth (about 0.5 g/kg). A maximum level of 94.6 mg/100 ml was reached within 40 minutes in treated volunteers compared to 36.4 mg/100 ml in untreated volunteers. The normal concentration of urea in the blood plasma of man is approximately 0.26 mg/ml (range: 20 to 30 mg/100 ml).

Urea is formed metabolically through a cyclic mechanism. Free ammonia arising from the oxidative deamination of glutamate in liver mitochondria combines with carbon dioxide to form carbamoyl phosphate. The carbamoyl group is transferred to ornithine to form citrilluline, which in turn reacts with aspartate to produce arginosuccinate. This is hydrolyzed enzymatically to liberate free arginine and femorata. The femorata returns to the pool of tricarboxylic acid cycle intermediates, while the arginine is cleaved by anginose to produce urea and ornithine.

The so-called aerolytic animals excrete urea as the major end-product of amino acid metabolism. Included in this group are mammals, elasmobranch, amphibia and Chelonia. Genetic deficiency of any of the enzymes required in the urea cycle produces protein intolerance, elevated amounts of blood ammonia, metabolic disturbances, neurological symptoms and brain damage. The development of the urea cycle enzymes in the fetus varies with the species. The pig fetus is able to synthesize urea at a very early stage, but the rat fetus acquires this ability only at a later period.

Urea is an end product of protein and ammonia metabolism in humans and a 70 kg adult excretes urea in the amount of 25-30 g/day (350-420 mg/kg/day). An individual consuming a high protein diet will excrete about 90 percent of the dietary nitrogen as urea whereas the percentage excreted as urea is less with a highly restricted nitrogen intake. The ability of the kidney to remove urea from the blood provides one method of assessing renal function, or more specifically, glomerular filtration capacity. However, the measurement of blood urea nitrogen (BUN) may be affected by poor nutrition and hepatotoxicity, which are common effects of many toxicants. Glomerular filtration rate can be also be determined by the renal clearance of creatinine, inulin, p-aminohippuric acid (PAH) and phenolsulfophthalein.

Urea had long been used as a dietary supplement for ruminants and in 1949, it was demonstrated that urea could serve as a nitrogen source in weanling rats as well. Similar utilization of urea has now been shown in rabbit, chick, pig, horse, and man. Bacterial action in the gastrointestinal tract, particularly in the colon, produces ammonia which is absorbed and mixed with the metabolic pool of nitrogen, where some may be utilized for protein synthesis. Urea nitrogen can contribute part of the amino acid requirements in man when the diet provides sufficient glucose for nonessential amino acid synthesis and utilization of urea nitrogen has been demonstrated both in malnourished children and adults. It has been estimated that the potential contribution of urea or ammonium salts to protein synthesis in man is less than 10 percent.

Therapeutic Uses

Urea is approved for several therapeutic uses in humans with relatively few toxicities. Urea is used primarily as an osmotic agent for inducing diuresis and reducing intraoccular and intracranial pressure (Ureaphil, 30% urea solution). Intravenous doses of 1-1.5 g/kg urea (30% urea solution) are considered optimal for neurosurgical procedures with no adverse effects. In addition, urea is approved by the FDA for topical use as (i) an anesthetic for the treatment of mouth and throat inflammation (10-15% urea gel, liquid or solution), (ii) a topical agent to debride necrotic and infected tissues, i.e. fingernails and toenails (2-40% formulations), and (iii) an active ingredient formulated within moisturizers (10-15% urea) for use in the prophylaxis and treatment of dry skin disorders. It is also used in the treatment of sickle-cell anemia and to ammoniate dentrifices as well as a basic ingredient in the synthesis of medically important compounds such as barbiturates and urethanes.

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40733303	Smith, S. (1986) Dermal Sensitization Study in Guinea Pigs with Unocal Plus: Laboratory Identification No.: Study 480-2781. Unpublished study prepared by American Biogenics Corp. 27 p.
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40733305	Smith, S. (1986) Acute Dermal Toxicity Study in Rabbits with Unocal Plus: Laboratory Identification No.: Study 480-2778. Unpublished study prepared by American Biogenics Corp. 12 p.
40733306	Smith, S. (1986) Primary Dermal Irritation in Rabbits with Unocal Plus: Laboratory Identification No.: Study 480-2779. Unpublished study prepared by American Biogenics Corp. 13 p.
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ATTACHMENT 1

Review of Six Acute Toxicity Studies and Two Literature Reviews on Urea.
Review PP# 8F3662 (Memorandum: S. Stolzenberg, June 30, 1989).

An electronic version of this document is not available. See the hard copy file.

ATTACHMENT 2

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ATTACHMENT 4

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An electronic version of this document is not available. See the hard copy file.

ATTACHMENT 5

Urea (Enfrost, 42.9% a.i.): Reevaluation of mammalian acute toxicity studies (OPPTS Test Guidelines 870.1100, 870.1200, 870.1300, 870.2400, 870.2500, and 870.2600) submitted by Unocal Corporation in Support of Registration. PC Code: 085702. DP Barcode: D277687. (Memorandum: M. Centra, August 28, 2001).

An electronic version of this document is available and stored under the following Toxicology Record Number (TXR#): 0050171.

ATTACHMENT 6

Food and Drug Administration, Department of Health and Human Services, code of federal regulations (Parts 170 to 199, Revised as of April 1, 2001). 21 CFR Part 184.1923; Urea, page 549.

ATTACHMENT 7

U.S. Environmental Protection Agency/Office of Pesticide Programs and Toxic Substances, Pesticide Fact Sheet (August 23, 1995).

An electronic version of this document is not available. See the hard copy file.

<u>ATTACHMENT 8</u>

Environmental Protection Agency, Federal Register Vol. 60, No. 163, Rules and Regulations. 40 CFR Part 180; Urea: Exemption From the Requirement of a Tolerance [PP-8F3662/R1176; FRL-4178-2] RIN 2070-AB78 (August 23, 1995).